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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/661,161	09/13/2000	Mary Chen	M-9181-2C US	2159

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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 07/12/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/661,161	Applicant(s) Chen et al.
	Examiner Vera Afremova	Art Unit 1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 22, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 20-25* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1 and 20-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1 and 20-25 are pending and under examination. Claims 2-19 were canceled by applicants. [Paper No. 2 filed 9/13/2000].

Information Disclosure Statement

The submitted reference AR has been considered on the merits and the copy of the IDS form is attached herein. Please, provide a copy of the reference AS {The information disclosure statement filed 9/13/2000 [Paper No. 3]} for a proper consideration. The parent application is presently missing the copy of AS reference. We apologize for related inconveniences.

Response to Arguments

Applicants' arguments filed 4/22/2002 have been fully considered but they are not all found persuasive for the reasons below.

Double Patenting

The rejection of claims 1 and 20-25 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-16 and 23-26 of U.S. Patent No. 5,856,179 [IDS-AG] has been withdrawn in the light of applicants' arguments related to restriction requirement and election made in the parent application 08/208,888 now US 5,856,179.

Claims 1 and 20-25 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,180,401 [A] as explained in the prior office action. The Terminal Disclaimer [Paper No. 9 filed 4/22/2002] is not

proper because the person who signed the Terminal Disclaimer has failed to state his capacity to sign for the business entity.

Claim Rejections - 35 USC § 112

Claims 1 and 20-25 remain rejected under 35 U.S.C. 112, *second paragraph*, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as explained in the prior office action and for the reasons below.

Claim 1 is rendered indefinite by the phrase "inclusive" because the meaning of this limitation remains uncertain as claimed and as disclosed. Applicants argue that this phrase is intended to include the limits or extremes of glucose concentrations. Yet, the claimed method does not particularly points out that the inclusion of limits and extremes is necessarily required but it is rather drawn to the inclusion of glucose concentrations between two claimed limits. Further, it is uncertain when the intended limits and extremes would be used, if required. The recitation of this phrase renders the claim at least redundant and, thus, is indefinite.

The claim 2 is rendered indefinite by the phrase "medium contains excess amino acids" because it is unclear in excess to what amount additional amino acids are required as claimed. Applicants argue that the intended concentrations are disclosed in the as-filed specification (page 11, last par.). Yet, the "excess" amounts, if any, are not claimed. The metes and bounds of the excess as intended can not be determined as claimed.

Claim 21 appears to lack antecedent basis for "**the** initial cell density" in the method of claim 1.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 20-22, 24 and 25 remain rejected under 35 U.S.C. 102(b) as being anticipated by Glaken et al. [IDS-AT] or by JP 1-101882 [IDS-AJ] in the light of Waymoth [IDS-BG] as explained in the prior office action and for the reasons below.

The claims are directed to a method of growing animal cells in a fed batch system wherein the method comprises culturing the cells by controlling glucose concentration between about 0.02 -0.2 g/L during culturing wherein a starting osmolarity is 280-302 mOsm. Some claims are further drawn to the use of an initial cell density between about $3x10^5$ and $1.5x10^6$ cells/ml or to the use mammalian cells or to the use of animal cells comprising nucleic acid encoding polypeptide or the use of flow injection analysis for glucose control in the method of culturing animal cells.

The cited references are relied upon as explained in the prior office action and repeated herein.

Glaken et al. [IDS-AT] disclose a method of growing mammalian cells in a fed batch system (page 1388, col. 1, par. 2) wherein the method comprises culturing the cells in an animal culture medium by controlling glucose concentration of 0.1 mM or about 0.02 g/L during

culturing (See culturing animal cells between 100 and 200 hours at Fig. 9). The cited reference clearly teaches an importance of lowering/adjusting glucose concentration until 0.1 mM during culturing period (page 1386, col. 1, par. 3) and the use of initial density or inoculum of mammalian cells of about $1.5x10^6$ cells/ml (page 1388, col.1, par. 1) which is between $3x10^5$ and $1.5x10^6$ cells/ml as presently claimed. The animal cells in the method of the cited reference comprise a nucleic acid encoding polypeptide such as DNA, for example. The cited reference teaches the use of on-line automated glucose control (fig. 2) as a glucose control by flow injection analysis of the claimed method (page 17, line 28).

JP 1-101882 [IDS-AJ] teaches a method of growing animal cells in a perfusion system wherein the method comprises culturing the cells by controlling glucose concentration above 0.01 mM but less than 3 mM (see translation page 3) which is between 0.02 -0.2 g/L as presently claimed. And the cited reference teaches the use of initial cell density of $5x10^5$ cell/ml (translation page 7, par. 1) which is between $3x10^5$ and $1.5x10^6$ cells/ml as required for the claimed method. The perfusion system of the cited reference (translation page 4, par. 3) appears to be identical to the claimed fed-batch system in the light of substantially similar, if not identical, definitions which encompass supplying nutrients "continuously or in discrete increments" (current specification page 5, line 30). The animal cells of the cited reference are mammalian cells or mouse-human hybridoma which comprise nucleic acid encoding a polypeptide such as IgG1 (translation page 6, par. 2) as required for the cells of the claimed method.

Although the cited references are silent with regard to initial osmolarity of about 280-302 mOsm for the culture media or culturing system, they teach the use of regular animal media in the method for growing animal cells. It is well known that the osmolarity of regular commercially available animal media is within the claimed range of 280-320 mOsm (see table 7 of the reference by Waymoth [IDS-BG]). Thus, the cited methods are reasonably expected to inherently comprise the use of osmolarity of regular culture media such as between 280-320 mOsm at least at the starting moment as required for the presently claimed method.

With regard to the reference by Glaken et al. [IDS-AT] (see response page 6-7) applicants argument that the cited method for growing animal cells includes the use of various glucose concentration at the variety of time periods, is not found persuasive because the claimed method is not limited by any time intervals by it is rather encompasses controlling glucose concentration during culturing of animal cells. Moreover, both the starting and the final glucose concentrations as shown on the Figure 9 of the cited reference are within the claimed ranges, for example: from about 0.5 mM (0.09 g/L) to about 0.01 mM (0.02 g/L).

With regard to the cited patent JP 1-101882 (see response pages 7-8) applicants arguments directed to the use of "perfusion" system rather than the use fed-batch system are not convincing because the perfusion system of the cited reference (translation page 4, par. 3) appears to be identical to the claimed fed-batch system in the light of substantially similar, if not

identical, definitions which encompass supplying nutrients "continuously or in discrete increments" (see specification page 5, line 30).

Applicants arguments that the cited references do not recognize the importance of the initial osmolarity of about 280-330 mOsm (see response pages 8-9) are not convincing because the methods of the cited references encompass the use of regular and/or commercially available animal culture media and it is well known that the regular and/or commercially available animal culture media are characterized by osmolarity of about 280-330 mOsm as clearly taught by Waymoth [IDS-BG]. Thus, the cited methods are reasonably expected to inherently comprise the use of osmolarity of regular culture media such as between 280-320 mOsm at least at the starting or initial moment of culturing animal cells as required for the presently claimed method. Applicants appear to argue that the cited references do not clearly disclose step of measuring osmolarity. However, the claimed method neither comprise steps of measuring osmolarity nor it is limited to the particular osmolarity values during culturing of animal cells.

Applicants' argument that the reference by Waymoth [IDS-BG] teaches a wide range of initial osmolarity for animal culture media such as between 288 to 820 mOsm and, thus, it teaches away (see response page 9, last line), is not correct. The cited paragraph 2 at col. 2 at page 199 of the reference by Waymoth discloses the osmolarity values of 288-320 mOsm but not 288-820 mOsm as argued.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glaken et al. [IDS-AT] or JP 1-101882 [IDS-AJ] in the light of Waymoth [IDS-BG] taken with Kurano et al. [IDS-BK] and Kurano et al. [IDS-BJ] as explained in the prior office action and for the reasons below.

The claims 1, 20-22, 24 and 25 as explained above. The claim 23 is further dawn to the use of CHO cells in the claimed method of growing animal cells.

All cited references are relied upon as explained in the prior office action and repeated herein.

The reference Glaken et al. [IDS-AT] and JP 1-101882 [IDS-AJ] are relied upon as explained above for the disclosure of a method of culturing mammalian cells by maintaining glucose concentration between 0.02 -0.2 g/L in a fed batch system wherein the method encompasses the use of a regular animal culture medium with initial osmolarity of 280-302 mOsm in the light of the Waymoth [IDS-BG] teaching. The cited references are lacking particular disclosure related to the use of CHO cells in the claimed method of culturing animal cells.

The references by Kurano et al. [IDS-BK] and Kurano et al. [IDS-BJ] are relied upon for the disclosure of optimal grow requirements of mammalian cells such as CHO in batch and fed-batch systems.

For example: Kurano et al. [IDS-BJ] teaches a maximum grow rate of CHO cells at lowest glucose concentration of about 0.01-0.25 g/L (see Fig. 3) in batch system and/or a maximum viable cell count at glucose concentration below about 0.5 g/L in fed-batch system (Fig. 6).

And the reference by Kurano et al. [IDS-BK] teaches that the best growth of CHO cells is observed when osmolarity is about 320 mOsm (see abstract).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute CHO cells of the secondary references {Kurano et al. [IDS-BK], Kurano et al. [IDS-BJ]} for the mammalian cells in the methods of growing animal cells of the primary references {Glaken et al. [IDS-AT], JP 1-101882 [IDS-AJ]} with a reasonable expectation of success in growing CHO cells because the cited prior art references teaches the use of the same growth conditions requirements for mammalian cells including CHO cells. One of skill in the art would have been motivated to use animal culture media with the osmolarity value of about 280-320 mOsm for growing mammalian cells because commercially available animal culture media are standardized for the osmolarity of about 280-320 mOsm {Waymoth [IDS-BG]}. Moreover, the prior art teaches that the best growth of mammalian cells such as CHO cells, for example, is observed at 320 mOsm {Kurano et al. [IDS-BK]}. One of

skill in the art would have been motivated to control glucose concentration within the claimed ranges during culturing of animal cells for the benefit of maximizing the growth and product synthesis and for minimizing waste accumulation {Glaken et al. [IDS-AT]; JP 1-101882 [IDS-AJ]}. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

With regard to the references by Kurano et al. [IDS-BK] (response pages 11-12) applicants appears to argue that it fails to recognize the importance of starting osmolarity of 230-320 mOsm. This is not true because this references clearly teaches that the best growth of CHO cells occurs at 320 mOsm (see abstract) which is the presently claimed value of osmolarity. The paragraph, which is cited by applicants for the support of arguments, demonstrates an isolated result in the whole series of studies which leads the authors to the conclusion that the osmolarity of 320 mOsm is the best value unlike applicants' interpretations.

With regard to the reference by Kurano et al. [IDS-BJ] (response page 12, last par.) applicants appear to argue that the culturing of CHO cells is demonstrated at various glucose concentrations including the values outside of the presently claimed range. However, a large range of glucose concentration has been applied by Kurano et al. in order to conclude that the

lowest concentration such as that which is presently claimed is the best for growing CHO cells as demonstrated on the Fig. 3.

In response to applicants' arguments (response pages 11-13) against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (see response page 13, last par.), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants' argument that none of the references provide specific motivation to combine the use of a starting osmolarity of about 280-320 mOsm with the controlling glucose concentration during culturing between about 0.02 -0.2 g/L, is not convincing. The references by Glaken et al. [IDS-AT], JP 1-101882 [IDS-AJ] and Waymoth [IDS-BG] teach the use of the same values of glucose concentration and starting osmolarity for growing mammalian cells as presently claimed. Further the references by Kurano et al. [IDS-BK] and Kurano et al. [IDS-BJ]

demonstrate that the same value of osmolarity and glucose as presently claimed are the best for growing CHO cells which are presently claimed. Therefore, all cited references are in the same field of endeavor and seek to solve the same problems as the instant application and claims, and one of skill in the art is free to select components available in the prior art. In re Winslow, 151 USPQ 48 (CCPA, 1966).

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651

July 10, 2002.

IRENE MARX
PRIMARY EXAMINER